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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100819-1 WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE 03/01329	International filing date *(day/month/year)* 26.08.2003	Priority date *(day/month/year)* 29.08.2002
International Patent Classification (IPC) or both national classification and IPC C07D211/26		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.03.2004	18.06.2004
Nam and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Usuelli, A Telephone No. +49 89 2399-7366

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE 03/01329

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-46 as published

Claims, Numbers

1-11 as published

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 8,10

   because:

   ☒ the said international application, or the said claims Nos. 8,10 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

   see separate sheet

R It m III

Claims 8 and 10 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(i) PCT.

Re Item V

1- Reference is made to the following documents cited in the search report:

D1: WO 94 13639 A1
D2: WO 00 25786 A1
D3: WO 00 02859 A1
D4: WO 02 051807 A1
D5: WO 00 20389 A1
D6: THOMAS RYCKMANS ET AL.: 'First Dual NK1 Antagonists-Serotonin Reuptake Inhibitors: Synthesis and SAR of a New Class of Potential Antidepressants' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS vol. 12, no. 2, January 2002, pages 261 - 264, XP002974383

2- Novelty
Present compounds of formula (I) differ from the compounds of d1 and d6 at least on account of the naphthyl group and from the compounds of d3,d4,d5 and d6 mainly on account of the moiety linking the piperidine and the naphthyl ring (present group - CH2N(R2)CO-).
There is a general overlap between present formula (I) and the formula (I) of d2 when (in d2) R6 and R7 taken together form a benzo ring. However, d2 does not disclose any single compound wherein R6 and R7 form a ring. Hence, there are no examples in d2 of naphthylamide derivatives. Thus, present compounds can be taken as a novel selection over d2 on account of the naphthyl moiety.
Since all the claims relate to the compounds of formula (I), the requirements of Art. 33.2 are met.

3- Inventive step
3.1- The applicant seems to have set himself the task of providing compounds having both neurokinin 1 (NK1) antagonist activity and serotonin reuptake inhibitory activity (SRI).

Documents d1,d3,d4,d5 and relate to compounds which modulate the tachykinins receptors. It appears that only d6 discloses compounds having both NK1 antagonist activity and SRI inhibitory activity.
D6 is therefore regarded as the closest state of the art.
For the scope of assessing the inventive activity during the international phase it is accepted that present compounds of formula (I) indeed possess the claimed activities.
The objective technical problem can therefore be taken as the provision of alternative compounds having both (NK1) antagonist activity and SRI inhibitory activity.

3.2- The compounds of d6 differ from present compounds on account of various features. In particular, they lack the naphthyl group and they have a different chain linking the piperidine to the other part of the molecule.
Although some naphthalene derivatives are disclosed in d3, d4 and d5, it appears that the skilled person would not find from the teaching of these documents any useful hint for modifying in the opportune manner the compounds of d6 thereby arriving at present compounds of formula (I), for the following reasons. As already indicated above, the compounds of d3 to d5 do not present the double activity of the present compounds and the compounds of d6. Hence, the skilled person would not combine the teachings relating to compounds having different activities. Furthermore, the compounds of d3 to d5 contain various structural differences from present compounds such as longer chain between the piperidine and the naphthyl ring and an additional aryl group attached to this chain. Hence, even taking into account of the teaching of these documents it appears that the skilled person would not arrive at the present invention in an obvious manner.